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WO 03/002548 A1

(54) Title: A PROCESS FOR THE PREPARATION OF CHIRAL GLUCOCORTICOID RECEPTOR AGENTS

(57) Abstract: The present invention relates to the preparation of chiral glucocorticoid receptor agents via biaryl atropisomers.

A PROCESS FOR THE PREPARATION OF
CHIRAL GLUCOCORTICOID RECEPTOR AGENTS

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Technical Field

The present invention relates to a novel process for the preparation of chiral selective glucocorticoid receptor agents.

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Background of the Invention

The glucocorticoid receptor (GR) has an essential role in regulating human physiology and immune response. Steroids which interact with GR have been shown to be potent antiinflammatory agents. Steroidal GR ligands, however, have side effects associated with chronic dosing believed to be the result of cross-reactivity with other steroid receptors such as estrogen, progesterone, androgen, and mineralocorticoid receptors which have somewhat homologous ligand binding domains. Therefore, nonsteroidal agents selective for GR are actively being researched for the treatment of inflammation, inflammatory disease, immune and autoimmune diseases.

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SUMMARY OF THE INVENTION

The present invention is directed to a process for preparing biaryl atropisomers that are used to prepare chiral GR agents. The process proceeds through a chirality transfer from a stereogenic center of a secondary alcohol to the biaryl stereogenic axis via regioselective intramolecular migration. This methodology allows for the preparation of a single biaryl atropisomer in high yield with high diastereoselectivity which subsequently leads to the synthesis of chiral glucocorticoid receptor agents.

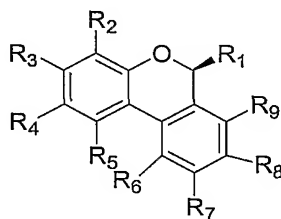
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In particular, the process is used to prepare chiral 5-substituted-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinolines wherein (5S)-5-allyl-10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinoline is a preferred chiral GR agent.

30

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention is directed to a process for the preparation of biaryl atropisomers that can be used for preparation of compounds of formula (I)



(I),

wherein

R₁ is selected from alkenyl, alkyl, alkynyl and aryl, wherein alkenyl is preferred and wherein allyl is most preferred;

R₂, R₃ and R₄ are each independently selected from hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

R₂ and R₃ or R₃ and R₄ together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from aryl, cycloalkyl and heterocycle, wherein hydrogen is preferred for each of R₂, R₃ and R₄;

R₅ is selected from hydrogen, alkenyl, alkenyloxy, alkoxy, alkoxycarbonyloxy, alkoxysulfonyloxy, alkyl, alkylcarbonyloxy, alkylsulfonyloxy, alkynyl, alkynyloxy, aryl, arylalkoxy, arylalkoxycarbonyloxy, aryloxy, arylsulfonyloxy, haloalkoxy, haloalkylcarbonyloxy, haloalkylsulfonyloxy, halogen, heterocycle and (NR_CR_D)carbonyloxy, wherein alkoxy and haloalkylsulfonyl are preferred and wherein methoxy and trifluoromethanesulfonate are most preferred;

R_C and R_D are each independently selected from hydrogen and alkyl;

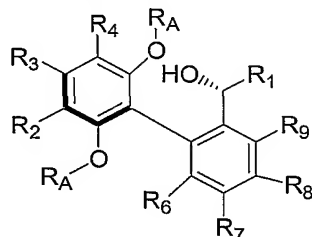
R₆, R₇, R₈ and R₉ are each independently selected from hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

R₆ and R₇ or R₇ and R₈ or R₈ and R₉ together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from aryl, cycloalkyl and heterocycle, wherein hydrogen is preferred for each of R₆ and R₇; R₈ and R₉ together with the carbon atoms to which they are attached, together form a ring wherein the ring is a heterocycle is preferred and wherein R₈ and R₉ together with the carbon atoms to which they

are attached, together form a ring wherein the ring 4,6,6-trimethyl-1,2,3,6-tetrahydropyridinyl is most preferred;

wherein the process comprises the steps of:

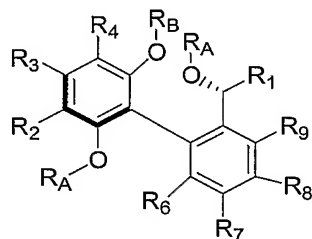
(a) treating a compound of formula (Ia)



(Ia),

with a base in a first solvent wherein R_A is a hydroxy protecting group;

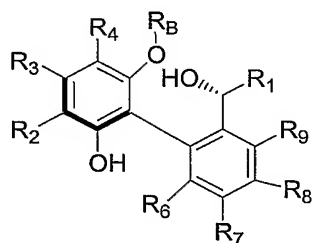
(b) treating the product of step (a) with an electrophile to provide a compound of formula (Ib);



(Ib),

wherein R_B is selected from alkoxycarbonyl, alkoxysulfonyl, alkenyl, alkyl, alkylcarbonyl, alkylsulfonyl, alkynyl, arylalkoxycarbonyl, arylalkyl, arylsulfonyl, haloalkyl, haloalkylcarbonyl, haloalkylsulfonyl and $(NR_C R_D)$ carbonyl, wherein alkyl and haloalkylsulfonyl are preferred and methyl and trifluoromethylsulfonyl are most preferred; R_C and R_D are each independently selected from hydrogen and alkyl;

(c) treating the compound of formula (Ib) with a hydroxy deprotecting reagent in a second solvent to provide a compound of formula (Ic); and



(Ic)

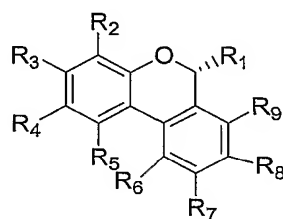
(d) treating the compound of formula (Ic) with an azo reagent and a phosphine reagent in a third solvent to provide the compound of formula (I).

5 According to another embodiment, the present invention further comprises the steps of the process described above wherein step (a) is conducted from about -5 °C to about 25 °C; isolating the product of step (b) by pouring step (b) into saturated ammonium chloride solution; stirring the solution; separating the aqueous phase from the organic phase; washing the organic phase with brine; drying the organic phase over sodium sulfate; concentrating the organic phase to provide an oil; dissolving the oil in heptane; extracting the heptane with acetonitrile; treating the heptane with charcoal; and concentrating the heptane to provide a compound of formula (Ib); step (c) is conducted between 18 °C and about 25 °C for about 12 to 36 hours; isolating the product of step (c) by pouring step (c) into a saturated solution of ammonium chloride; stirring the solution; adding tert-butyl methyl ether to the solution; 10 stirring the solution for about 5 to 20 minutes; separating the aqueous phase from the organic phase; washing the organic phase with brine; drying the organic phase over sodium sulfate; concentrating the organic phase to provide a solid; suspending the solid in isopropanol:heptane 1:12.5 for 1 to 3 hours; cooling the isopropanol:heptane 1:12.5 to -5 °C to about 5 °C; and filtering the isopropanol:heptane 1:12.5 to provide a compound of formula (Ic); in step (d) the product of step (c) and the triphenylphosphine are dissolved in the tetrahydrofuran at a temperature between 18 °C and about 25 °C; the tetrahydrofuran may optionally be cooled to about -5 °C to about 15 °C; and the diisobutyl azodicarboxylate is added to the tetrahydrofuran over about 0.25 to 3 hours while maintaining the temperature of the tetrahydrofuran from -5 °C to about 25 °C; isolating the product from step(d) by 20 concentrating the tetrahydrofuran to about 1/4 to 1/3 of original volume; adding heptane to the tetrahydrofuran; cooling the tetrahydrofuran/heptane mixture to about -5 °C to about 5 °C; allowing the tetrahydrofuran/heptane mixture to stand for 12 to 24 hours; filtering the tetrahydrofuran/heptane mixture; repeating concentration, cooling and filtering until small amount of solid precipitates out of the tetrahydrofuran/heptane mixture; concentrating the tetrahydrofuran/heptane mixture to provide crude product of step (d); purifying the crude 30

product of step (d) by flash chromatography to provide the product of step (d); and recrystallizing the product of step (d) from isopropanol.

The process of the present invention is particularly useful for preparing (5S)-5-allyl-10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinoline and (5S)-5-allyl-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinolin-10-yl trifluoromethanesulfonate.

According to yet another embodiment, the present invention discloses a process for the preparation of a compound having formula (II)



(II),

wherein

R₁ is selected from the group consisting of alkenyl, alkyl, alkynyl and aryl;

R₂, R₃ and R₄ are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl and halogen; or

R₂ and R₃ or R₃ and R₄ together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

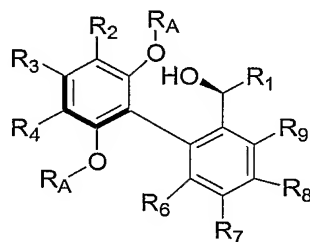
R₅ is selected from the group consisting of hydrogen, alkenyl, alkenyloxy, alkoxy, alkoxy carbonyloxy, alkoxy sulfonyloxy, alkyl, alkyl carbonyloxy, alkyl sulfonyloxy, alkynyl, alkynyloxy, aryl, arylalkoxy, arylalkoxy carbonyloxy, aryl sulfonyloxy, haloalkoxy, haloalkyl carbonyloxy, haloalkyl sulfonyloxy, halogen, heterocycle and (NR_CR_D)carbonyloxy; and

R₆, R₇, R₈ and R₉ are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl and halogen; or

R_6 and R_7 or R_7 and R_8 or R_8 and R_9 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

wherein said process comprises the steps of:

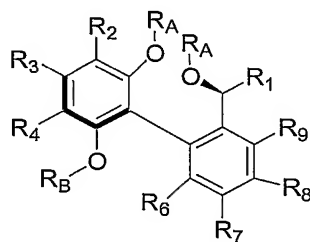
- 5 (a) treating a compound of formula (IIa)



(IIa),

with a base in a first solvent, wherein R_A is a hydroxy protecting group and R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above

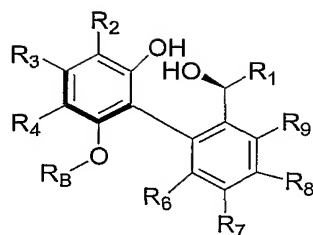
- 10 (b) treating the product of step (a) with an electrophile to provide a compound of formula (IIb)



(IIb),

- 15 wherein R_B is selected from the group consisting of alkoxycarbonyl, alkoxysulfonyl, alkenyl, alkyl, alkylcarbonyl, alkylsulfonyl, alkynyl, arylalkoxycarbonyl, arylalkyl, arylsulfonyl, haloalkyl, haloalkylcarbonyl, haloalkylsulfonyl and $(NR_C R_D)$ carbonyl wherein R_C and R_D are selected from the group consisting of hydrogen and alkyl; and R_A , R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above;

- 20 (c) treating the compound of formula (IIb) with a hydroxy deprotecting reagent in a second solvent to provide a compound of formula (IIc)

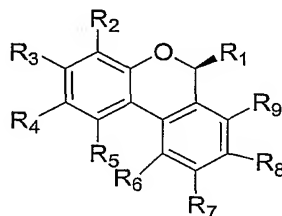


(IIc)

wherein R_B , R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above; and

- (d) treating the compound of formula (IIc) with an azo reagent and a phosphine
 5 reagent in a third solvent to provide the compound of formula (II).

According to a further embodiment, the present invention discloses a process for the preparation of a compound having formula (I)



(I),

wherein

R_1 is selected from the group consisting of alkenyl, alkyl, alkynyl and aryl, wherein alkenyl is preferred and wherein allyl is most preferred;

R_2 , R_3 and R_4 are each independently selected from the group consisting of hydrogen,
 15 alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

R_2 and R_3 or R_3 and R_4 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle, wherein hydrogen is preferred for each of R_2 , R_3 and R_4 ;

R_5 is selected from the group consisting of hydrogen, alkenyl, alkenyloxy, alkoxy, alkoxy-carbonyloxy, alkoxy-sulfonyloxy, alkyl, alkyl-carbonyloxy, alkyl-sulfonyloxy, alkynyl, alkynyloxy, aryl, arylalkoxy, arylalkoxy-carbonyloxy, aryloxy, aryl-sulfonyloxy, haloalkoxy, haloalkyl-carbonyloxy, haloalkyl-sulfonyloxy, halogen, heterocycle and $(NR_C R_D)$ -carbonyloxy, wherein alkoxy is preferred and methoxy is most preferred;

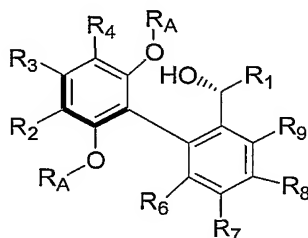
R_C and R_D are each independently selected from hydrogen and alkyl; and

R₆, R₇, R₈ and R₉ are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

R₆ and R₇ or R₇ and R₈ or R₈ and R₉ together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle, wherein hydrogen is preferred for each of R₆ and R₇; R₈ and R₉ together with the carbon atoms to which they are attached, together form a ring wherein the ring is a heterocycle is preferred, wherein R₈ and R₉ together with the carbon atoms to which they are attached, together form a ring wherein the ring 4,6,6-trimethyl-1,2,3,6-tetrahydropyridinyl is most preferred;

wherein said process comprises the steps of:

(a) treating a compound of formula (Ia)



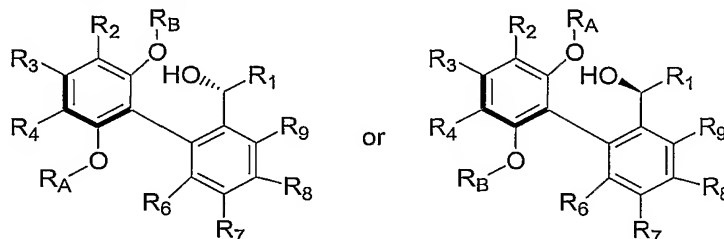
(Ia),

with at least two molar equivalents of a hydroxy deprotecting reagent in a first solvent, wherein R_A is a hydroxy protecting group and R₁, R₂, R₃, R₄, R₆, R₇, R₈ and R₉ are as defined above, to provide a compound of formula (Ia) wherein R_A is hydrogen;

(b) treating the product of step (a) with an azo reagent and a phosphine reagent in a second solvent, a preferred second solvent is tetrahydrofuran.

As used throughout this specification and the appended claims, the following terms have the following meanings:

The term "single biaryl atropisomer" as used herein, refers to a biaryl atropisomer of general formula (Ib) or (IIb) shown below:



(Ib)

(IIb)

wherein $R_1, R_2, R_3, R_4, R_6, R_7, R_8$ and R_9 are as defined in formula (I) for a biaryl atropisomer of general formula (Ib); $R_1, R_2, R_3, R_4, R_6, R_7, R_8$ and R_9 are as defined in formula (II) for a biaryl atropisomer of general formula (IIb); R_A is a hydroxy protecting group and R_B is selected from alkoxycarbonyl, alkoxysulfonyl, alkenyl, alkyl, alkylcarbonyl, alkylsulfonyl, alkynyl, arylalkoxycarbonyl, arylalkyl, arylsulfonyl, haloalkyl, haloalkylcarbonyl, haloalkylsulfonyl and $(NR_C R_D)$ carbonyl.

The term "azo reagent" as used herein, refers to a reagent, $R-N=N-R$, wherein R is selected from alkoxycarbonyl and cycloalkyloxycarbonyl. Representative examples of azo reagent include, but are not limited to, diethyl azodicarboxylate, di-tert-butyl azodicarboxylate, diisopropyl azodicarboxylate, dimethyl azodicarboxylate and dicyclohexyl azodicarboxylate. A preferred azo reagent is selected from diethyl azodicarboxylate, di-tert-butyl azodicarboxylate and diisopropyl azodicarboxylate. A most preferred azo reagent is diisopropyl azodicarboxylate.

The term "base" as used herein, refers to any molecular moiety that can remove the hydrogen from a secondary alcohol. Representative examples of base include, but are not limited to, alkoxides such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide and potassium tert-butoxide; hydrides such as sodium hydride, potassium hydride and lithium hydride; amides such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide and sodium bis(trimethylsilyl)amide. A preferred base is potassium tert-butoxide.

The term "electrophile" as used herein, refers to any molecular moiety that contains a carbon atom or a sulfur atom wherein the carbon or sulfur atom can accept a pair of electrons. Representative examples of electrophile include, but are not limited to, methyltriflate, methyltosylate, dimethylsulfate and trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide; acid chlorides such as acetyl chloride, propionyl chloride, trimethylacetyl chloride and dimethylcarbamyl chloride; alkenyl halides such as allyl bromide; alkyl halides such as iodomethane, iodoethane, trifluoromethyl iodide, perfluoroethyl iodide, benzyl bromide and benzyl chloride; alkynyl halides such as propargyl bromide; anhydrides such as acetic anhydride, trifluoromethyl anhydride and di-tert-butyl dicarbonate; chloroformates such as benzyl chloroformate, ethyl chloroformate and isopropyl

chloroformate; sulfonyl chlorides such as methanesulfonyl chloride (mesyl chloride), para-toluenesulfonyl chloride (tosyl chloride) and phenylsulfonyl chloride; and sulfonic anhydrides such as trifluoromethanesulfonic anhydride (triflic anhydride). A preferred electrophile is selected from trifluoro-N-phenyl-N-

5 [(trifluoromethyl)sulfonyl]methanesulfonamide and iodomethane.

The term "hydroxy protecting group" as used herein, refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures.

Preferred hydroxy protecting groups of the present invention include, but are not limited to, alkylcarbonyl, (alkyl)(diaryl)silyl, (trialkyl)silyl, (triaryl)silyl and (triarylalkyl)silyl.

10 Representative examples of hydroxy protecting groups include, but are not limited to, acetyl, ethylcarbonyl, propylcarbonyl, tert-butylcarbonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, methyldiphenylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl and triphenylsilyl. A preferred hydroxy protecting group is tert-butyldimethylsilyl.

15 The term "hydroxy deprotecting reagent" as used herein, refers to a reagent that removes a hydroxy protecting group. Representative examples of hydroxy deprotecting reagents includes, but is not limited to, a source of fluoride anion such as tetrabutylammonium fluoride, potassium fluoride and hydrogen fluoride; inorganic acids such as hydrochloric acid and hydrobromic acid; organic acids such as acetic acid and
20 trifluoroacetic acid; a source of aqueous hydroxide ion such as aqueous potassium hydroxide, aqueous sodium hydroxide, aqueous potassium carbonate and aqueous sodium bicarbonate. A preferred hydroxy deprotecting reagent is tetrabutylammonium fluoride.

The term "phosphine reagent" as used herein refers to $(R_E)_3P$ wherein R_E is selected from alkyl and aryl. Representative example of $(R_E)_3P$ include, but are not limited to,
25 tributylphosphine, tri-tert-butylphosphine, triisobutylphosphine, triisopropylphosphine, tripropylphosphine, triethylphosphine, trimethylphosphine, tris(4-methylphenyl)phosphine, tris(4-methoxyphenyl)phosphine, tris(4-chlorophenyl)phosphine, tris(4-bromophenyl)phosphine and triphenylphosphine. A preferred phosphine reagent is triphenylphosphine.

The term "first solvent" as used herein, refers to any organic solvent that will allow the reaction in step (a) and the reaction in step (b) to proceed to completion or substantially to completion. A preferred first solvent is tetrahydrofuran.

5 The term "second solvent" as used herein, refers to any organic solvent that will allow the reaction in step (c) to proceed to completion or substantially to completion. A preferred second solvent is tetrahydrofuran.

The term "third solvent" as used herein, refers to any organic solvent that will allow the reaction in step (d) to proceed to completion or substantially to completion. A preferred third solvent is tetrahydrofuran.

10 The term "alkenyl" as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

15 The term "alkenyloxy" as used herein, refers to an alkenyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkenyloxy include, but are not limited to, allyloxy, 2-butenyloxy and 3-butenyloxy.

20 The term "alkoxy" as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

25 The term "alkoxycarbonyl" as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl.

The term "alkoxycarbonyloxy" as used herein, refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxycarbonyloxy include, but are not limited to, methoxycarbonyloxy, ethoxycarbonyloxy, and tert-butoxycarbonyloxy.

30 The term "alkoxysulfonyl" as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein.

Representative examples of alkoxysulfonyl include, but are not limited to, methoxysulfonyl, ethoxysulfonyl and propoxysulfonyl.

The term "alkoxysulfonyloxy" as used herein, refers to an alkoxysulfonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

5 Representative examples of alkoxysulfonyloxy include, but are not limited to, methoxysulfonyloxy, ethoxysulfonyloxy and propoxysulfonyloxy.

The term "alkyl" as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-
10 pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term "alkylcarbonyl" as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl,
15 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term "alkylcarbonyloxy" as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, propionyloxy and (2,2-dimethylpropanoyl)oxy.

20 The term "alkylsulfonyl" as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited to, methylsulfonyl and ethylsulfonyl.

The term "alkylsulfonyloxy" as used herein, refers to an alkylsulfonyl group, as
25 defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkylsulfonyloxy include, but are not limited to, methylsulfonyloxy and ethylsulfonyloxy.

The term "alkynyl" as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple
30 bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butyne, 2-pentyne, and 1-butyne.

The term "alkynyloxy" as used herein, refers to an alkynyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkynyloxy include, but are not limited to, 2-propynyloxy and 2-butyloxy.

5 The term "aryl" as used herein, refers to a phenyl group. The aryl groups of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkoxy, alkoxycarbonyl, alkoxysulfonyl, alkyl, alkylcarbonyl, alkynyl, cyano, haloalkoxy, haloalkyl, halogen, nitro, -NR_CR_D and (NR_CR_D)carbonyl.

10 The term "arylalkoxy" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of arylalkoxy include, but are not limited to, benzyloxy, 2-phenylethoxy and 5-phenylpentyloxy.

The term "arylalkoxycarbonyl" as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylalkoxycarbonyl include, but are not limited to, 15 benzyloxycarbonyl.

The term "arylalkoxycarbonyloxy" as used herein, refers to an arylalkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of arylalkoxycarbonyloxy include, but are not limited to, benzyloxycarbonyloxy.

20 The term "arylalkyl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl and 2-phenylethyl.

25 The term "aryloxy" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of aryloxy include, but are not limited to, phenoxy, 4-chlorophenoxy and 3, 4-dimethylphenoxy.

30 The term "arylsulfonyl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of arylsulfonyl include, but are not limited to, phenylsulfonyl and 4-methylphenylsulfonyl.

The term "arylsulfonyloxy" as used herein, refers to an arylsulfonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of arylsulfonyloxy include, but are not limited to, phenylsulfonyloxy and 4-methylphenylsulfonyloxy.

5 The term "carbonyl" as used herein, refers to a -C(O)- group.

The term "cyano" as used herein, refers to a -CN group.

The term "cycloalkyl" as used herein, refers to a saturated cyclic hydrocarbon group containing from 4 to 6 carbons. Examples of cycloalkyl include cyclobutyl, cyclopentyl and cyclohexyl.

10 The term "cycloalkyloxy" as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of cycloalkyloxy include, but are not limited to, cyclobutyloxy, and cyclohexyloxy.

The term "cycloalkyloxycarbonyl" as used herein, refers to cycloalkyloxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined
15 herein. Representative examples of cycloalkyloxycarbonyl include, but are not limited to, cyclohexyloxycarbonyl.

The term "halo" or "halogen" as used herein, refers to -Cl, -Br, -I or -F.

The term "haloalkoxy" as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein.
20 Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy.

The term "haloalkyl" as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-
25 fluoroethyl, trifluoromethyl and pentafluoroethyl.

The term "haloalkylcarbonyl" as used herein, refers to a haloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of haloalkylcarbonyl include, but are not limited to, trifluoromethylcarbonyl.

30 The term "haloalkylcarbonyloxy" as used herein, refers to a haloalkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

Representative examples of haloalkylcarbonyloxy include, but are not limited to, trifluoromethylcarbonyloxy.

The term "haloalkylsulfonyl" as used herein, refers to a haloalkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein.

5 Representative examples of haloalkylsulfonyl include, but are not limited to, trifluoromethylsulfonyl and pentafluoroethylsulfonyl.

The term "haloalkylsulfonyloxy" as used herein, refers to a haloalkylsulfonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

10 Representative examples of haloalkylsulfonyloxy include, but are not limited to, trifluoromethylsulfonyloxy and pentafluoroethylsulfonyloxy.

The term "heterocycle" or "heterocyclic" as used herein, refers to a monocyclic or bicyclic ring system. Monocyclic ring systems are exemplified by any 3- or 4-membered ring containing a heteroatom independently selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms wherein the heteroatoms are independently selected from nitrogen, oxygen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6- and 7-membered ring have from 0-3 double bonds.

Representative examples of monocyclic ring systems include, but are not limited to, azetidiny, azepanyl, aziridiny, diazepiny, 1,3-dioxolanyl, dioxanyl, dithianyl, furyl, imidazolyl, imidazoliny, imidazolidiny, isothiazolyl, isothiazoliny, isothiazolidiny, 20 isoxazolyl, isoxazoliny, isoxazolidiny, morpholiny, oxadiazolyl, oxadiazoliny, oxadiazolidiny, oxazolyl, oxazoliny, oxazolidiny, piperaziny, piperidiny, pyranyl, pyraziny, pyrazolyl, pyrazoliny, pyrazolidiny, pyridiny, pyrimidiny, pyridaziny, pyrroly, pyrroliny, pyrrolidiny, tetrahydrofuranyl, tetrahydropyridiny, tetrahydrothienyl, tetraziny, tetrazolyl, thiadiazolyl, thiadiazoliny, thiadiazolidiny, thiazolyl, thiazoliny, thiazolidiny, 25 thienyl, thiomorpholiny, 1,1-dioxidothiomorpholiny (thiomorpholine sulfone), thiopyranyl, triaziny, triazolyl, and trithianyl. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazolyl, benzodioxiny, 30 benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, benzofuranyl, benzopyranyl, benzothiopyranyl, cinnoliny, indazolyl, indolyl, 2,3-dihydroindolyl, indoliziny,

naphthyridinyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, phthalazinyl, pyranopyridinyl, quinolinyl, quinoliziny, quinoxaliny, quinazolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, and thiopyranopyridinyl.

5 The heterocycles of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkoxy, alkoxycarbonyl, alkoxysulfonyl, alkyl, alkylcarbonyl, alkynyl, cyano, haloalkoxy, haloalkyl, halogen, nitro, oxo, -NR_CR_D and (NR_CR_D)carbonyl. Representative examples of substituted heterocycles includes, but is not limited to, 4,6,6-trimethyl-1,2,3,6-tetrahydropyridinyl.

The term "nitro" as used herein, refers to a -NO₂ group.

10 The term "-NR_CR_D" as used herein, refers to two groups, R_C and R_D, which are appended to the parent molecular moiety through a nitrogen atom. R_C and R_D are each independently selected from hydrogen and alkyl. Representative examples of -NR_CR_D include, but are not limited to, amino, methylamino, dimethylamino, ethylmethylamino and diethylamino.

15 The term "(NR_CR_D)carbonyl" as used herein, refers to a -NR_CR_D group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of (NR_CR_D)carbonyl include, but are not limited to, aminocarbonyl, (methylamino)carbonyl, (dimethylamino)carbonyl, (ethylmethylamino)carbonyl, and (diethylamino)carbonyl.

20 The term "(NR_CR_D)carbonyloxy" as used herein, refers to a (NR_CR_D)carbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of (NR_CR_D)carbonyloxy include, but are not limited to, aminocarbonyloxy, (methylamino)carbonyloxy, (dimethylamino)carbonyloxy, (ethylmethylamino)carbonyloxy and (diethylamino)carbonyloxy.

25 The term "oxo" as used herein, refers to a =O moiety.

The term "sulfonyl" as used herein, refers to a -SO₂- group.

30 The term "(alkyl)(diaryl)silyl" as used herein, refers to an alkyl group, as defined herein, and two aryl groups, as defined herein, appended to the parent molecular moiety through a silane atom. Representative examples of (alkyl)(diaryl)silyl, include, but are not limited to, methylphenylsilyl and tert-butylphenylsilyl.

The term "(trialkyl)silyl" as used herein, refers to three independent alkyl groups, as defined herein, appended to the parent molecular moiety through a silane atom.

Representative examples of (trialkyl)silyl, include, but are not limited to, trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl and tert-butyl dimethylsilyl.

The term "(triaryl)silyl" as used herein, refers to three independent aryl groups, as defined herein, appended to the parent molecular moiety through a silane atom.

Representative examples of (triaryl)silyl, include, but are not limited to, triphenylsilyl.

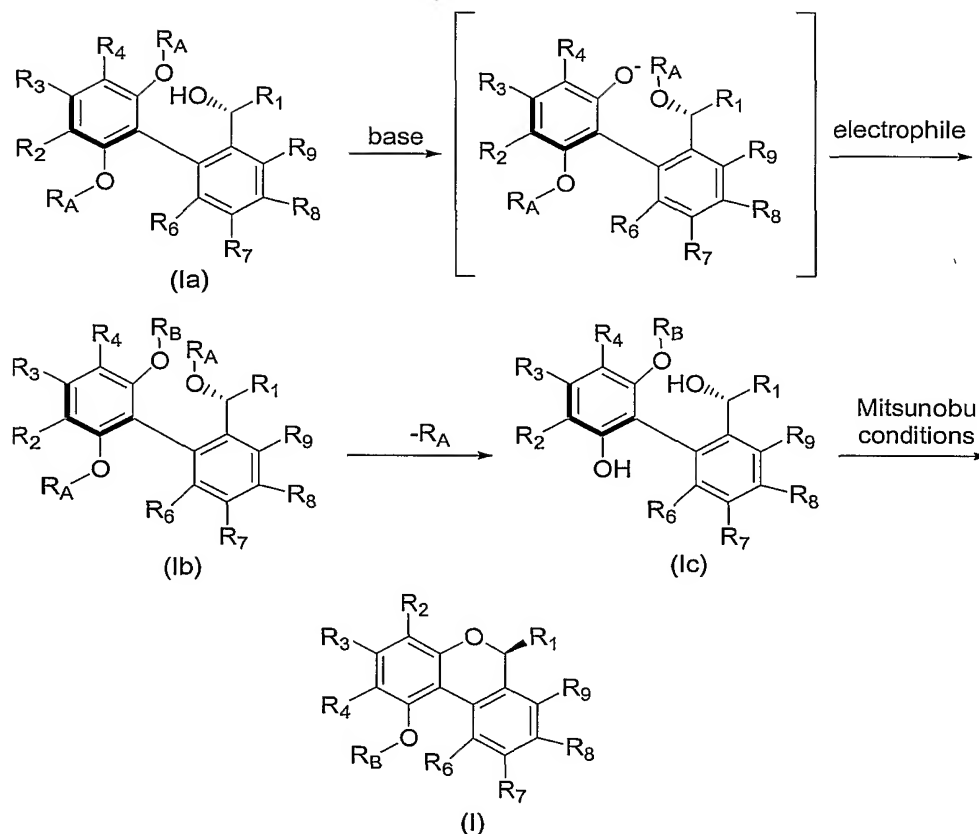
The term "(triarylalkyl)silyl" as used herein, refers to three independent arylalkyl groups, as defined herein, appended to the parent molecular moiety through a silane atom. Representative examples of (triarylalkyl)silyl, include, but are not limited to, tribenzylsilyl.

Synthetic Processes

Abbreviations which have been used in the descriptions of the Schemes and the Examples that follow are: t-Bu for tert-butyl; DIAD for diisopropyl azodicarboxylate; DMSO for dimethylsulfoxide, DIBAL or DIBAL-H for diisobutylaluminum hydride; EtOAc for ethyl acetate; HPLC for high pressure liquid chromatography; IPA for isopropyl alcohol; Ipc for isopinocampheyl; MTBE for tert-butyl methyl ether; TBAF for tetrabutylammonium fluoride; TBS for tert-butyl dimethylsilyl; TBSCl for tert-butyl dimethylsilyl chloride; THF for tetrahydrofuran; Tf for $-S(O)_2CF_3$; TLC for thin layer chromatography; and TMS for trimethylsilyl.

The present invention will be better understood in connection with the following synthetic Schemes.

Scheme 1

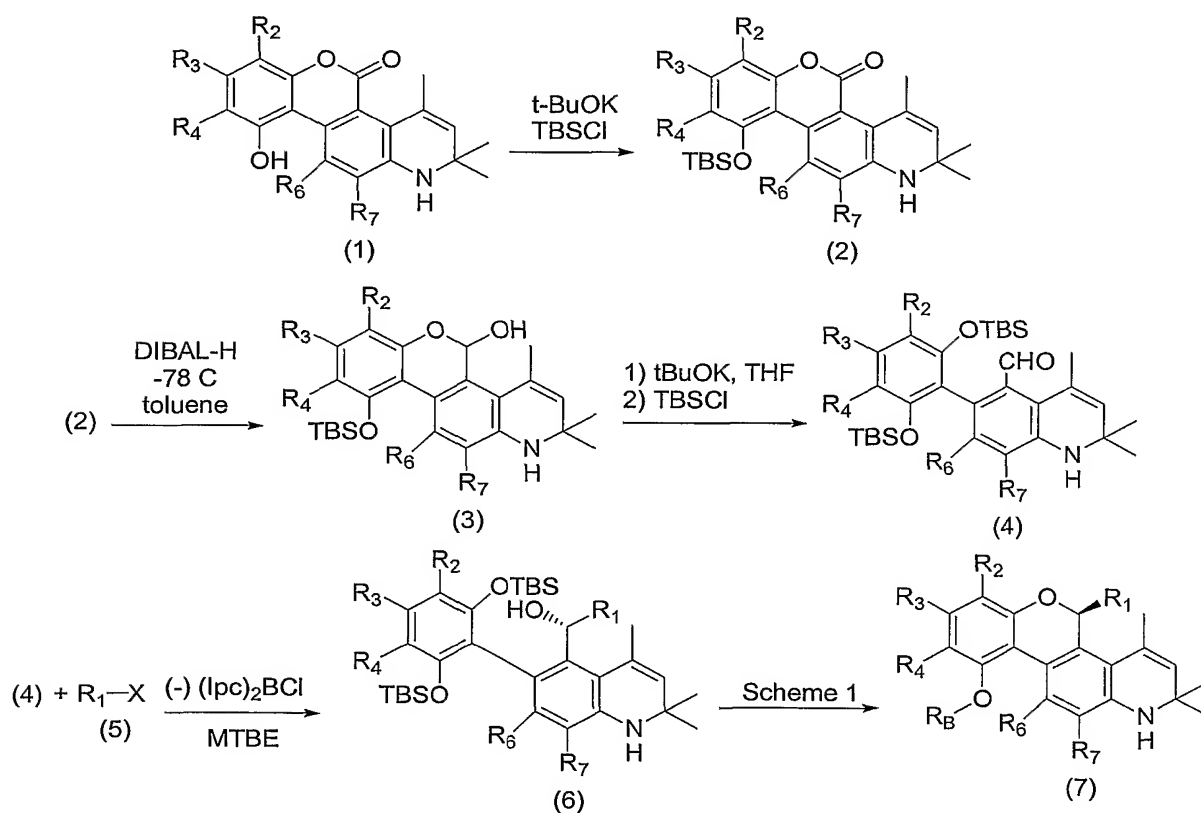


Scheme 1 describes the general applicability of the present invention to preparing compounds of general formula (I). Compounds of general formula (Ia), wherein base, electrophile, R_B, R₁, R₂, R₃, R₄, R₆, R₇, R₈ and R₉ are as defined herein and R_A is a hydroxy protecting group, as defined herein, wherein a preferred hydroxy protecting group is tert-butyldimethylsilyl, can be treated with a base that is sufficiently basic enough to remove a proton from a secondary alcohol, a preferred base is potassium tert-butoxide, in a solvent such as tetrahydrofuran to provide an intermediate phenolic anion. The base removes the proton from the secondary alcohol facilitating migration of the hydroxy protecting group, R_A, spacially nearest to the alkoxide resulting in the generation of a phenolic anion which can be treated with any electrophile, as defined herein, to provide an atropisomer of general formula (Ib). The two protecting groups, R_A, can then be removed under standard conditions depending on R_A to provide compounds of general formula (Ic). The phenolic oxygen, in compounds of general formula (Ic), is spacially orientated for nucleophilic backside attack on

the carbon atom attached to the hydroxy group. This spacial arrangement in the presence of an azo and a phosphine reagent, as defined herein, in a solvent such as tetrahydrofuran facilitates an intramolecular displacement reaction providing compounds of general formula (I).

5 As would be understood by one skilled in the art, the opposite enantiomer of compounds of general formula (Ia) will provide the opposite enantiomer of compounds of formula (I).

Scheme 2

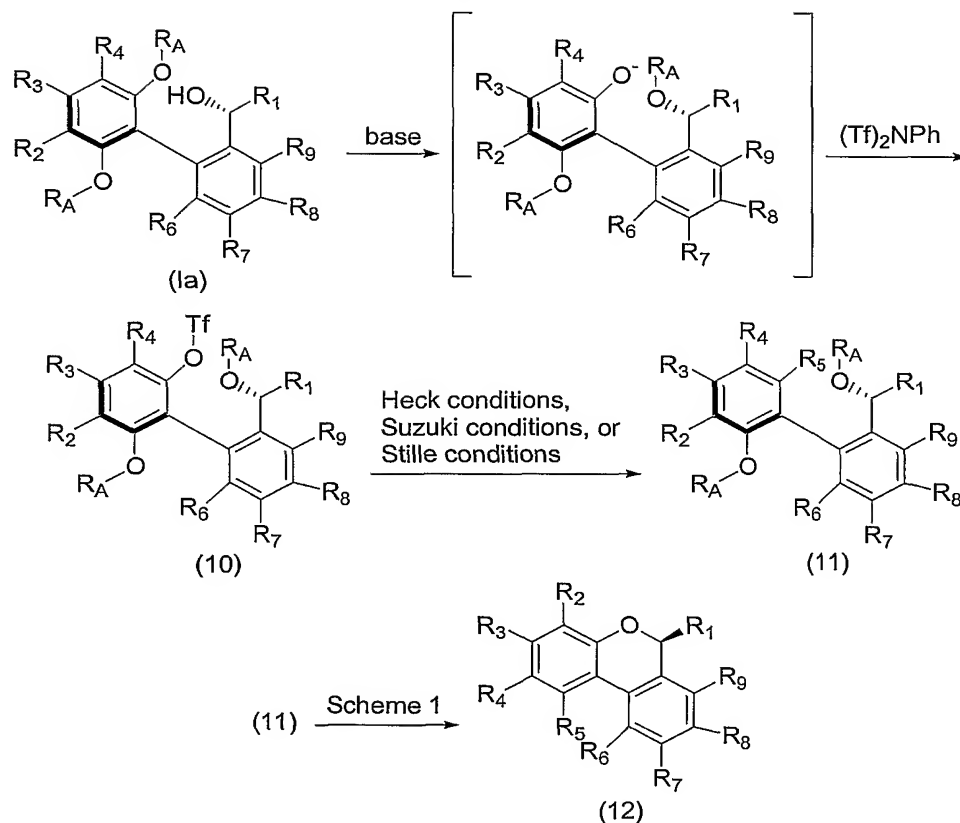


Compounds of general formula (7), wherein $R_B, R_1, R_2, R_3, R_4, R_6$ and R_7 are as defined in formula (I), can be prepared as described in Scheme 2. 1,2-Dihydro-5H-chromeno[3,4-f]quinolin-5-ones of general formula (1), prepared as described in International Publication Number WO 99/41256 and which is incorporated by reference herein, can be treated with a base such as potassium tert-butoxide and a hydroxy protecting reagent such as

tert-butyldimethylsilyl chloride to provide lactones of general formula (2). Lactones of general formula (2) can be treated with a reducing agent such as diisobutylaluminum hydride in toluene at -78 °C to provide lactols of general formula (3). Lactols of general formula (3) can be treated with a base such as potassium tert-butoxide and then treated with any
5 electrophile such as tert-butyldimethylsilyl chloride to provide bis(silyl) aldehydes of general formula (4). Bis(silyl) aldehydes of general formula (4) can be treated with a chiral chelating agent such as (-) (Ipc)₂BCl and a compound of general formula (5) wherein X is MgBr, Li or TMS in a solvent such as tert-butyl methyl ether to provide chiral alcohols of general formula (6). Chiral alcohols of general formula (6) can be processed as described in Scheme 1 or the
10 Examples contained herein to provide compounds of general formula (7).

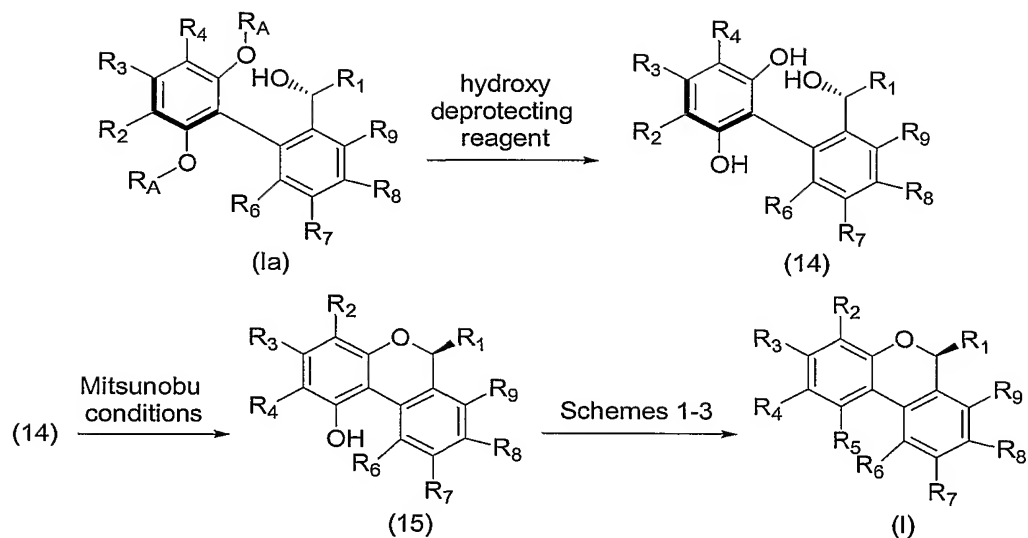
As would be understood by one skilled in the art, treating bis(silyl) aldehydes of general formula (4) with (+) (Ipc)₂BCl and a compound of general formula (5) will provide the opposite enantiomer of compounds of general formula (6) and processing the opposite enantiomer of compounds of general formula (6) as described in Scheme 1 will provide the
15 opposite enantiomer of compounds of general formula (7).

Scheme 3



Compounds of general formula (12), wherein R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined in formula (I) and R_5 is selected from alkenyl, alkyl, alkynyl, aryl and heterocycle, can be prepared as described in Scheme 3. Compounds of general formula (Ia) can be treated with a base and then an electrophile wherein the electrophile is trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide or trifluoromethanesulfonic anhydride as described in Scheme 1 or the Examples contained herein to provide triflates of general formula (10). Triflates of general formula (10) can be treated under Heck, Suzuki or Stille conditions, which are well known to those of skill in the art, to provide compounds of general formula (11). Compounds of general formula (11) can be processed as described Scheme 1 or the Examples contained herein to provide compounds of general formula (12).

Scheme 4



Alternatively, Compounds of general formula (I), wherein electrophile, R_A, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are as defined herein, can be prepared as described in Scheme 4.

- 5 Compounds of general formula (Ia) can be treated with a hydroxy deprotecting reagent such as tetrabutylammonium fluoride, when R_A is selected from (alkyl)(diaryl)silyl, (trialkyl)silyl, (triaryl)silyl or (triarylalkyl)silyl wherein tert-butyldimethylsilyl preferred, to provide triols of general formula (14). Triols of general formula (14) can be treated under Mitsunobu conditions as described in Scheme 1 to provide compounds of general formula (15).
- 10 Compounds of general formula (15) can be processed as described in Schemes 1-3 to provide compounds of general formula (I).

The present invention is now described by the following Examples in connection with particularly preferred embodiments of Schemes 1-4. The following Examples are not intended to limit the scope the present invention. The present invention covers all

15 alternatives, modifications and equivalents included in the appended claims. Thus, the following Examples illustrate a preferred practice of the invention, it being understood that the Examples are for the purposes of illustration of certain preferred embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

20

Example 1

10-{[tert-butyl(dimethyl)silyl]oxy}-2,2,4-trimethyl-1,2-dihydro-5H-chromeno[3,4-f]quinolin-5-one

10-hydroxy-2,2,4-trimethyl-1,2-dihydro-5H-chromeno[3,4-f]quinolin-5-one (HCl salt) (131.6g), prepared as described in WO99/41256, in THF (2.6L) in a 5L 4-necked flask fitted with N₂ inlet, temperature probe and overhead stirrer was treated with t-BuOK in approximately 20g portions over 15 minutes (103.4g total) at 0 °C under a N₂ atmosphere. The cooled reaction mixture was stirred for 30 minutes. The mixture was treated with TBSCl in approximately 20g portions over 15 minutes. The reaction was monitored by TLC, EtOAc:heptane (2:3), and/or HPLC, Zorbax Rx-C8 4.6mm x 25cm column; mobile phase 90%H₂O (0.1% H₃PO₄) : 10%CH₃CN (0.1% H₃PO₄) to 30:70 over 15 minutes, then to 10:90 over 20 minutes before ramping back to 10:90 over 2 minutes; 45 minute run; flow rate of 1mL/minute; UV detection at 225nm. Retention times: starting material-17.6 minutes; product-29.9minutes, until starting material was consumed, about 30 minutes. The reaction mixture was quenched with 50% NH₄Cl solution (1L) and extracted with EtOAc (1L). The organic layer was washed with brine (500mL) before concentrating to a crude solid (180.8g). The crude solid was slurried in CH₃CN (900mL) with heating until an even suspension was obtained. The suspension was then cooled to approximately 0 °C, filtered and washed with cold CH₃CN. The wet cake was dried at 40 °C in a vacuum oven to yield 82.2g of the title compound as a yellow solid. The mother liquors were concentrated to a solid (69g) and re-slurried in CH₃CN (250mL). A second crop was collected and dried to yield an additional 11.8g (81% combined yield). A small sample was crystallized from CH₃CN. Anal. calcd for C₂₅H₃₁NO₃Si: C, 71.22; H, 7.41; N, 3.32. Found: C, 68.38; H, 7.45; N, 3.16; ¹H NMR (CDCl₃) δ 0.32 (6H, s), 1.05 (9H, s), 1.33 (6H, s), 2.12 (3H, s), 4.26 (1H, br), 5.58 (1H, br), 6.75 (1H, d), 6.94 ~ 6.97 (2H, m), 7.17 (1H, t), 8.75 (1H, d); ¹³C NMR (CDCl₃) δ -3.9, 18.4, 21.2, 25.9, 28.3, 50.4, 77.2, 110.1, 111.3, 115.4, 118.2, 120.0, 124.2, 126.9, 126.9, 127.3, 131.7, 132.0, 144.9, 151.9, 153.2, 160.1 with 3 peaks overlapping; HRMS-FAB: calcd m/z 422.2151, found 422.2137.

Example 2

10-{[tert-butyl(dimethyl)silyl]oxy}-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinolin-5-ol

The product from Example 1 (37.1g) in toluene (1.8L) under N₂ in a 3L 3-necked flask equipped with an overhead mechanical stirrer, addition funnel, and temperature probe was treated with diisobutylaluminum hydride in heptane (132mL) dropwise at -78 °C over 40 minutes. After complete addition, the reaction mixture was stirred at -78 °C and monitored by HPLC, Zorbax Rx-
5 C8 4.6mm x 25cm column; mobile phase 90%H₂O (0.1% H₃PO₄):10%CH₃CN (0.1% H₃PO₄) to 30:70 over 15 minutes, then to 10:90 over 20 minutes before ramping back to 10:90 over 2 minutes; 45 minute run; flow rate of 1mL/minute; UV detection at 225nm. Retention times: starting material-29.9 minutes; product-20.4 minutes, and/or TLC, EtOAc:heptane (2:3), until starting material was consumed, about 1 hour. Ethyl acetate (500mL) was added to quench any
10 excess DIBAL, cooling was removed and saturated Rochelle's salt solution (1L) was added. The quenched mixture warmed to room temperature with stirring. The stirring was continued until layers clearly separated. The organic layer was washed with brine (500mL) before concentrating to a solid. The isolated solid was dried at 40 °C in a vacuum oven to yield 41.2g of the title compound as a tan solid which was used in the next step without further purification. A small
15 reference sample was crystallized from CH₃CN. Anal. calcd for C₂₅H₃₃NO₃Si: C, 70.88; H, 7.85; N, 3.31. Found: C, 70.60; H, 7.84; N, 3.22; ¹H NMR [(CD₃)₂SO] δ 0.10 (3H, s) 0.24 (3H, s), 0.97 (9H, s), 1.08 (3H, s), 1.26 (3H, s), 2.24 (3H, s), 5.41 (1H, br), 6.07 (1H, br), 6.55 ~ 6.61 (4H, m), 6.91 (1H, d), 6.98 (1H, t), 7.99 (1H, d); ¹³C NMR [(CD₃)₂SO] δ -4.5, -4.2, 18.0, 22.8, 25.8, 28.2, 30.1, 49.7, 89.9, 111.2, 113.5, 113.7, 115.7, 116.4, 116.9, 126.2, 127.2, 128.2, 130.2, 132.4, 145.3,
20 151.0, 151.8 with 2 peaks overlapping; HRMS-FAB: calcd m/z 423.2230, found 423.2232.

Example 3

6-(2,6-bis{[tert-butyl(dimethyl)silyl]oxy}phenyl)-2,2,4-trimethyl-1,2-dihydroquinoline-5-carbaldehyde

25 The product from Example 2 (40.6g) in THF (800mL) in a 3L 3-necked flask fitted with N₂ inlet, temperature probe and overhead stirrer was treated with t-BuOK in approximately 10g portions over 5 minutes (32.3g total) at 0 °C under N₂. After complete addition, the mixture was stirred for 30 minutes at 0 °C and then treated with TBSCl in approximately 10g portions over 5 minutes (31.8g total). The reaction was monitored by
30 TLC, EtOAc:heptane (2:3), and/or HPLC, Zorbax Rx-C8 4.6mm x 25cm column; mobile phase 90%H₂O (0.1% H₃PO₄) : 10%CH₃CN (0.1% H₃PO₄) to 30:70 over 15 minutes, then to

10:90 over 20 minutes, held at 10:90 for 20 minutes before ramping back to 10:90 over 2 minutes; 65 minutes run; flow rate of 1.5mL/minute; UV detection at 225nm. Retention times: starting material-20.4minutes; product-34.9minutes, until starting material was consumed, about 30 minutes. The reaction mixture was quenched with 50% NH₄Cl solution (500mL) and extracted with EtOAc (500mL). The organic layer was washed with brine (500mL) before concentrating to crude solid (57.0g). The crude solid was slurried in methanol (230mL) with heating until an even suspension. The suspension was then cooled to approximately 0 °C, filtered and washed with cold methanol. The wet cake was dried in a vacuum oven at 40 °C to yield 36.1g of the title compound as a white solid. A small reference sample was crystallized from methanol. Anal. Calcd for C₃₁H₄₇NO₃Si₂: C, 69.22; H, 8.81; N, 2.60. Found: C, 69.00; H, 9.10; N, 2.60; ¹H NMR (CDCl₃) δ 0.01 (12H, s), 0.71 (18H, s), 1.28 (6H, s), 1.87 (3H, s), 3.94 (1H, br), 5.51 (1H, br), 6.52 (2H, d), 6.73 (1H, d), 6.88 (1H, d), 7.06 (1H, t), 10.07 (1H, s); ¹³C NMR (CDCl₃) δ -4.7, 17.7, 22.4, 25.2, 28.3, 50.3, 112.7, 117.4, 121.8, 123.1, 127.7, 128.3, 130.4, 131.9, 132.2, 134.5, 144.6, 154.5, 196.1 with 12 peaks overlapping; HRMS-FAB: calcd m/z 538.3173, found 538.3151.

Example 4

(1R)-1-[6-(2,6-bis{[tert-butyl(dimethyl)silyl]oxy}phenyl)-2,2,4-trimethyl-1,2-dihydroquinolin-5-yl]but-3-en-1-ol

(+) Chlorodiisopinocampheylborane(52.5g) in MTBE (1.8L) under N₂ in a 5L 4-necked flask fitted with N₂ inlet, addition funnel, temperature probe and overhead stirrer was treated with allylmagnesium bromide dropwise over 40-50 minutes (147mL) at -78 °C. After complete addition, the mixture was stirred for 2 hours (-78 °C) and then the mixture was treated with the product from Example 3 (44.0g dissolved in 400mL MTBE) dropwise while maintaining the reaction temperature -78 °C. The reaction was monitored by TLC, EtOAc:heptane (2:3), and/or HPLC, Zorbax Rx-C8 4.6mm x 25cm column; mobile phase 90%H₂O (0.1% H₃PO₄) : 10%CH₃CN (0.1% H₃PO₄) to 30:70 over 15 minutes, then to 10:90 over 20 minutes, held at 10:90 for 20 minutes before ramping back to 10:90 over 2 minutes; 65 minute run; flow rate of 1.5mL/minute; UV detection at 225nm. Retention times: starting material-34.9 minutes; product-34.3 minutes, until starting material was consumed, about 30-60 minutes. The reaction mixture was quenched with 5% NaHCO₃ solution (1L) and

extracted with hexanes (1L). The organic layer was washed with brine (500mL) before concentrated to a tan oil (102g). After sitting at room temperature open to the environment for 72 hours, the oil partially solidified. The crude oil/solid was slurried in hexanes (2-300mL), cooled under vacuum (0 °C) and filtered. The precipitate was washed with hexanes, dried in a vacuum oven at 40 °C to yield 10.5g. Additional precipitate was obtained from the cooled mother liquors to yield an additional 36.3g (94% potency yield) of the title compound as a white solid. The isolated product can be triturated with methanol to improve color and purity. A small reference sample was crystallized from methanol. Anal. Calcd for $C_{34}H_{53}NO_3Si_2$: C, 70.41; H, 9.21; N, 2.42. Found: C, 69.13; H, 8.76; N, 2.30; 1H NMR $[(CD_3)_2SO]$ δ -0.09 (3H, s), 0.04 (3H, s), 0.08 (3H, s), 0.10 (3H, s), 0.67 (9H, s), 0.68 (9H, s), 1.09 (3H, s), 1.15 (3H, s), 2.10 (1H, m), 2.15 (3H, s), 2.21 (1H, m), 4.01 (1H, d), 4.62 (1H, m), 4.72~4.80 (2H, m), 5.40 (1H, br), 5.62 (1H, m), 5.84 (1H, br), 6.51 (1H, d), 6.57~6.59 (3H, m), 7.13 (1H, t); ^{13}C NMR $[(CD_3)_2SO]$ δ -5.0, -4.8, -4.7, -4.6, 17.4, 17.5, 23.2, 25.1, 25.2, 26.6, 27.5, 40.1, 48.8, 17.7, 112.2, 112.6, 113.1, 115.3, 122.4, 122.9, 127.1, 128.3, 130.3, 131.8, 132.0, 137.6, 138.4, 145.9, 153.5, 154.3; ESI-MS: m/z 580 (M+H) $^+$, HRMS-FAB: calcd m/z 579.3564, found 579.3568.

Example 5

5-((1R)-1-{{tert-butyl(dimethyl)silyl}oxy}but-3-enyl)-6-(2-{{tert-butyl(dimethyl)silyl}oxy}-6-methoxyphenyl)-2,2,4-trimethyl-1,2-dihydroquinoline

A 1L three-necked round bottom flask was charged with the product from Example 4 (25g) in THF (1.37L) and treated with a 1M solution of t-BuOK (58 ml) dropwise over 20 minutes at 0 °C. The reaction was monitored by TLC, EtOAc:hexanes (2:3), and/or HPLC, Zorbax SB-CS; Flow rate: 1.5 ml/minute; 50:50 to 90:10 acetonitrile:water (0.1 % H_3PO_4) over 10 minutes, then 90:10 to 95:05 acetonitrile:water (0.1 % H_3PO_4) over 25 minutes; UV detection: 225 nm. Retention time for starting material 18.6 minutes; Retention time for the silyl group migration intermediate: 19.6 minutes. After the completion of the reaction was determined, iodomethane (6.4 ml) was added to the reaction mixture all at once. The ice-bath was removed and the mixture was allowed to warm to room temperature and stirred for two hours. Completion of the reaction was monitored with HPLC. HPLC conditions: Zorbax SB-CS; Flow rate: 1.5 ml/minute; 50:50 to 90:10 acetonitrile:water (0.1 % H_3PO_4) over 10 minutes, then 90:10 to 95:05

acetonitrile:water (0.1 % H₃PO₄) over 25 minutes; UV detection: 225 nm. Retention time for the silyl group migration intermediate: 19.6 minutes; Retention time for the methylation product: 20.6 minutes. The reaction mixture was poured into saturated NH₄Cl solution (500 ml) and stirred briefly. The organic layer was separated, washed with brine (500 ml), dried over NaSO₄, and concentrated to give an orange oil. Heptane (250 ml) was added to the oil residue to dissolve the crude product. The solution was extracted with CH₃CN (2X15 ml) and was treated with charcoal and concentrated to dryness to give 26.6g crude product as an oil residue. A small reference sample of the product was obtained by column chromatography purification eluting with heptane:ethyl acetate (95:2). ¹H NMR [(CD₃)₂SO] δ -0.22 (3H, s), -0.19 (3H, s), -0.17 (3H, s), 0.01 (3H, s), 0.78 (9H, s), 0.80 (9H, s), 1.06 (3H, s), 1.22 (3H, s), 2.23 (3H, s), 2.32 (1H, br), 2.54 (1H, br), 3.61 (3H, s), 4.66 (2H, m), 4.77 (1H, d), 5.33 (2H, s), 5.77 (1H, s), 6.46 (1H, d), 6.55 (2H, m), 6.68 (1H, d), 7.19 (1H, t); ¹³C NMR [(CD₃)₂SO] δ -5.5, -4.6, -4.5, -4.3, 17.8, 17.9, 25.8, 29.4, 41.4, 48.6, 55.1, 74.3, 104.6, 112.9, 115.8, 121.2, 122.5, 123.1, 127.1, 128.3, 130.1, 131.3, 137.5, 140.0, 146.4, 153.7, 158.6; ESI-MS: m/z 594 (M+H)⁺, HRMS-FAB: calcd m/z 593.3721, found 593.3699.

Example 6

2-{5-[(1R)-1-hydroxybut-3-enyl]-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl}-3-methoxyphenol

The product from Example 5 (26.0g) in THF (250 mL) was purged with nitrogen for 10 minutes at room temperature and then treated with a 1.0M TBAF solution all at once, a dark purple solution formed. The reaction mixture was stirred at room temperature overnight. The completion of the reaction was monitored with both HPLC and TLC. TLC: 40% EtOAc in Hexane, starting material R_f: 6.0, the desilylation product R_f: 3.0. HPLC conditions: Zorbax SB-CS; flow rate: 1.0 ml/minutes 90:10 to 30:70 acetonitrile : water (0.1 % H₃PO₄) over 15 minutes, then 30:70 to 10:90 acetonitrile : water (0.1 % H₃PO₄) over 20 minutes; UV detection at 225 nm. The reaction mixture was poured into a solution of saturated NH₄Cl (250 ml), stirred briefly and added MTBE (150 ml). The mixture was stirred for 5 minutes and the organic layer was separated. The organics were washed with brine (200 ml), dried over Na₂SO₄ and concentrated to dryness to give light yellow solid. The solid was then suspended in IPA (20 ml)/heptane (250 ml) at room temperature for two hours at room temperature, then cooled to 0 °C. The suspension was filtered to give 13.6 g of the title compound as a light yellow solid which was used in the

next step without further purification. ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 1.13 (3H, s), 1.18 (3H, s), 2.19 (3H, s), 2.27 (2H, m), 3.61 (3H, s), 4.14 (1H, d), 4.65 (1H, m), 4.75 (2H, d), 5.38 (1H, s), 5.48 (1H, m), 5.83 (1H, s), 6.49~6.55 (4H, m), 7.09 (1H, t), 9.02 (1H, s); ^{13}C NMR $[(\text{CD}_3)_2\text{SO}]$ δ 24.2, 27.6, 28.3, 40.1, 48.8, 55.4, 71.7, 102.5, 108.8, 113.2, 115.3, 119.3, 122.2, 122.7, 128.2, 130.4, 131.3, 131.6, 137.3, 139.2, 145.6, 155.8, 158.0; ESI-MS: m/z 366 ($\text{M}+\text{H}$) $^+$; HRMS-FAB: calcd m/z 365.1991, found 365.1989.

Example 7

(5S)-5-allyl-10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinoline

10 The product from Example 6 (10.0g) and triphenylphosphine (17.97g) in THF was stirred briefly at room temperature to dissolve the solids and then cooled to $-2\text{ }^\circ\text{C}$. The cooled solution was treated with DIAD (12.7 ml) in THF (135 ml) dropwise over about 1.5 hours while maintaining the temperature below $0\text{ }^\circ\text{C}$. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for two hours and then was slowly warmed to room temperature over a two hour period.

15 The reaction was monitored with HPLC, in case of incomplete reaction, more reagents could be added to the reaction mixture following the same sequence, i.e. addition of triphenylphosphine first followed by DIAD solution. HPLC conditions: Zorbax SB-CS; flow rate: 1.0 ml/minutes 90:10 to 30:70 acetonitrile : water (0.1 % H_3PO_4) over 15 minutes, then 30:70 to 10:90 acetonitrile : water (0.1 % H_3PO_4) over 20 minutes; UV detection at 225 nm.

20 Retention time: starting material diol: 15.5 minutes, the product allyl compound: 25.5 minutes, the by-product triphenylphosphine oxide. The solvent was concentrated under vacuum to about 300ml, heptane was added, and the mixture was cooled in the refrigerator overnight. The solid was filtered, the filtrate was further concentrated upon cooling when vacuum was applied. More solid was precipitated out. When the total volume of the filtrate was about 400 ml, the solid was filtered again. When the filtrate contained very small amounts of triphenylphosphine oxide, the filtrate was concentrated to an oil. The oil was purified by column chromatography with 5% EtOAc/hexane to give 6.05g (85% ee, which was determined by chiral HPLC using a Chiralcel OJ 4.6 x 250 mm column with hexane/ethanol as eluting solvents) of the title compound as an off-white foam. The % ee

25 was further improved by crystallization with IPA to 98.5% with 75% recovery. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_2$: C, 79.51; H, 7.25 and N, 4.03; Found: C, 79.26; H, 7.12 and N, 3.80; ^1H

30

NMR [(CD₃)₂SO] δ 1.16 (3H, s), 1.17 (3H, s), 2.18 (3H, s), 2.22 (1H, m), 2.46 (1H, m), 3.85 (3H, s), 5.01 (2H, m), 5.44 (1H, br s), 5.77 (1H, dd), 5.82 (1H, m), 6.10 (1H, br s), 6.52 (1H, d), 6.60 (1H, d), 6.70 (1H, d), 7.06 (1H, t) and 7.96 (1H, d); ¹³C NMR [(CD₃)₂SO] δ 23.8, 28.8, 28.9, 36.5, 49.7, 55.6, 73.4, 105.6, 110.5, 113.4, 113.4, 116.1, 116.4, 127.3, 117.3, 127.3, 127.7, 132.2, 133.8, 134.5, 145.8, 151.1, 156.4. APCI-MS: m/z 348 (M+H)⁺.

Example 8

2-{5-[(1R)-1-hydroxybut-3-enyl]-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl}benzene-1,3-diol

The product from Example 4 (1.0 g, 1.7 mmol) in THF (15 mL) and acetic acid (0.1 mL) was purged with N₂ for 10 minutes at room temperature and then treated with a 1.0 M solution of TBAF in THF (7.6 mL). The reaction mixture was stirred at room temperature overnight under N₂. HPLC indicated that the de-silylation was complete. The reaction mixture was poured into a solution of saturated NH₄Cl (30 mL) and stirred briefly before MTBE (30 mL) was added. After stirring for 5 minutes, the organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated to dryness to give light yellow solid. The solid was then recrystallized with EtOAc/heptane to give the title compound (520 mg) as an off-white solid. ¹H NMR [(CD₃)₂SO] δ 1.10 (3H, s), 1.22 (3H, s), 2.17 (3H, s), 2.23 (2H, m), 4.76~4.80 (3H, m), 5.12 (1H, d), 5.40 (1H, br), 5.52 (1H, m), 5.88 (1H, br), 6.38 (1H, dd), 6.43 (1H, dd), 6.53 (2H, m), 6.93 (1H, t), 8.92 (1H, s), 9.09 (1H, s); ¹³C NMR [(CD₃)₂SO] δ 23.3, 27.2, 28.6, 39.8, 48.9, 71.2, 107.1, 107.4, 113.0, 115.3, 119.3, 122.2, 122.5, 127.6, 129.6, 131.6, 132.2, 136.8, 138.3, 145.0, 154.8, 155.9; ESI-MS: m/z 352 (M+H)⁺; HRMS-FAB: calcd 351.1834, found 351.1829.

Example 9

(5S)-5-allyl-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinolin-10-ol

The product of Example 8 (0.8 g, 2 mmol) and triphenylphosphine (1.4 g, 5 mmol) in THF (50 mL) were treated with DIAD (1.0 mL, 5 mmol) in THF (1 mL) dropwise at 0 °C. After 30 minutes, the cooling bath was removed and the mixture was allowed to warm to room temperature with stirring. After 1 hour, reaction was complete by HPLC. Heptane was added and precipitated triphenylphosphine oxide was then filtered off. The filtrate was

concentrated and the residue purified by column chromatography with silica gel eluting with EtOAc/heptane to give the title compound as a solid (157 mg).

Example 10

5 (5S)-5-allyl-10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinoline

The product from Example 9 (157 mg) in THF (10 ml) was treated with a 1.0 M solution of tBuOK (1.0 ml) at 0 °C and then treated with iodomethane (0.1 ml). After stirring at room temperature for 2 hours, the mixture was poured into a solution of saturated NH₄Cl (15 mL) and stirred briefly before MTBE (15 mL) was added. After stirring for 5 minutes, 10 the organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography to give the title compound (134 mg). Anal. calcd for C₂₃H₂₅NO₂: C, 79.51; H, 7.25 and N, 4.03; Found: C, 79.26; H, 7.12 and N, 3.80; ¹H NMR [(CD₃)₂SO] δ 1.16 (3H, s), 1.17 (3H, s), 2.18 (3H, s), 2.22 (1H, m), 2.46 (1H, m), 3.85 (3H, s), 5.01 (2H, m), 5.44 (1H, br s), 5.77 (1H, dd), 5.82 (1H, m), 6.10 15 (1H, br s), 6.52 (1H, d), 6.60 (1H, d), 6.70 (1H, d), 7.06 (1H, t) and 7.96 (1H, d); ¹³C NMR [(CD₃)₂SO] δ 23.8, 28.8, 28.9, 36.5, 49.7, 55.6, 73.4, 105.6, 110.5, 113.4, 113.4, 116.1, 116.4, 127.3, 117.3, 127.3, 127.7, 132.2, 133.8, 134.5, 145.8, 151.1, 156.4; APCI-MS: m/z 348 (M+H)⁺.

20 Example 11

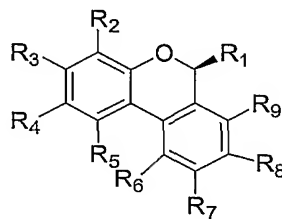
3-{[tert-butyl(dimethyl)silyl]oxy}-2-[5-((1R)-1-{[tert-butyl(dimethyl)silyl]oxy}but-3-enyl)-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl]phenyl trifluoromethanesulfonate

The product of Example 4 (1.74 g, 3.0 mmol) in THF (150 mL) at 0 °C was treated with a 1.0M solution of t-BuOK in THF (3.9 mL) dropwise while keeping the temperature 25 below at 0 °C. After migration was complete (as determined by HPLC), the mixture was treated with trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide (1.6 g, 4.5 mmol) in one portion. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stir for 6 hours. The reaction mixture was then poured into saturated NH₄Cl solution (150 mL), stirred briefly, and MTBE (80 mL) was added. The 30 organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated to an orange oil. The orange oil was dissolved in heptane (50 mL) and extracted with CH₃CN (5

mL, 2X) to remove color and impurities. The heptane layers were concentrated to dryness to give the title compound (1.8 g) as an oil. A small reference sample of the product was obtained as a colorless oil by column chromatography purification eluting with heptane:ethyl acetate (95:2). ¹H NMR (C₅D₅N) δ 0.11 (3H, s), 0.13 (3H, s), 0.14 (3H, s), 0.23 (3H, s), 0.89 (9H, s), 0.99 (9H, s), 1.34 (3H, s), 1.37 (3H, s), 2.41 (3H, s), 2.82 (2H, m), 5.02~5.09 (2H, m), 5.61 (H, m), 6.92 (1H, d), 7.02 (1H, m), 7.10 (1H, d), 7.18 (1H, d), 7.21 (NH, s) 7.39 (1H, m); ¹³C NMR [(CD₃)₂SO] δ -4.2, -4.0, -3.6, 18.3, 18.5, 25.0, 25.9, 26.5, 28.1, 28.4, 43.2, 49.9, 74.3, 113.2, 114.2, 116.1, 119.3, 120.2, 128.8, 130.2, 132.5, 133.3, 137.4, 140.2, 147.3, 156.0; MS (APCI) m/z: 713 (M+H)⁺; HRMS-FAB: calcd m/z 712.3133, found 712.3143.

What is claimed is:

1. A process for the preparation of a compound having formula (I)



(I),

5 wherein

R_1 is selected from the group consisting of alkenyl, alkyl, alkynyl and aryl;

R_2 , R_3 and R_4 are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

10 R_2 and R_3 or R_3 and R_4 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

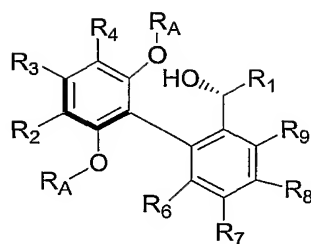
R_5 is selected from the group consisting of hydrogen, alkenyl, alkenyloxy, alkoxy, alkoxy-carbonyloxy, alkoxy-sulfonyloxy, alkyl, alkyl-carbonyloxy, alkyl-sulfonyloxy, alkynyl, alkynyloxy, aryl, arylalkoxy, arylalkoxy-carbonyloxy, aryloxy, arylsulfonyloxy, haloalkoxy, haloalkyl-carbonyloxy, haloalkyl-sulfonyloxy, halogen, heterocycle and $(NR_C R_D)$ -carbonyloxy
15 wherein R_C and R_D are each independently selected from the group consisting of hydrogen and alkyl; and

R_6 , R_7 , R_8 and R_9 are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

20 R_6 and R_7 or R_7 and R_8 or R_8 and R_9 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

wherein said process comprises the steps of:

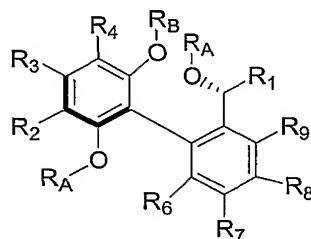
(a) treating a compound of formula (Ia) with a base in a first solvent



(Ia),

wherein R_A is a hydroxy protecting group and R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above;

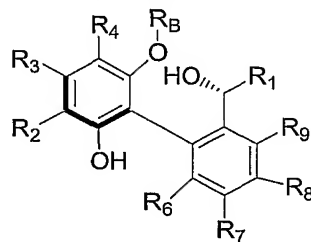
- 5 (b) treating the product of step (a) with an electrophile to provide a compound of formula (Ib)



(Ib),

- 10 wherein R_B is selected from the group consisting of alkoxycarbonyl, alkoxysulfonyl, alkenyl, alkyl, alkylcarbonyl, alkylsulfonyl, alkynyl, arylalkoxycarbonyl, arylalkyl, arylsulfonyl, haloalkyl, haloalkylcarbonyl, haloalkylsulfonyl and $(NR_C R_D)$ carbonyl; and R_A , R_C , R_D , R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above;

- (c) treating the compound of formula (Ib) with a hydroxy deprotecting reagent in a second solvent to provide a compound of formula (Ic)



(Ic)

wherein R_B , R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above; and

- (d) treating the compound of formula (Ic) with an azo reagent and a phosphine reagent in a third solvent.

2. The process according to claim 1 wherein
R₂, R₃, R₄, R₆ and R₇ are each hydrogen; and
R₈ and R₉ together with the carbon atoms to which they are attached, together form a
5 ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and
heterocycle.
3. The process according to claim 1 wherein
R₁ is alkenyl;
10 R₂, R₃, R₄, R₆ and R₇ are each hydrogen; and
R₈ and R₉ together with the carbon atoms to which they are attached, together form a
ring wherein the ring is heterocycle.
4. The process according to claim 1 wherein
15 R₁ is alkenyl;
R₂, R₃, R₄, R₆ and R₇ are each hydrogen; and
R₈ and R₉ together with the carbon atoms to which they are attached, together form a
ring wherein the ring is heterocycle wherein the heterocycle is 4,6,6-trimethyl-1,2,3,6-
tetrahydropyridinyl.
20
5. The process according to claim 1 wherein
R₁ is alkenyl;
R₂, R₃, R₄, R₆ and R₇ are each hydrogen;
R₅ is alkoxy; and
25 R₈ and R₉ together with the carbon atoms to which they are attached, together form a
ring wherein the ring is heterocycle wherein the heterocycle is 4,6,6-trimethyl-1,2,3,6-
tetrahydropyridinyl.
6. The process according to claim 1 wherein the compound of formula (I) is (5S)-5-allyl-
30 10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinoline.

7. The process according to claim 1 wherein
R₁ is alkenyl;
R₂, R₃, R₄, R₆ and R₇ are each hydrogen;
R₅ is haloalkylsulfonyloxy; and
- 5 R₈ and R₉ together with the carbon atoms to which they are attached, together form a ring wherein the ring is heterocycle wherein the heterocycle is 4,6,6-trimethyl-1,2,3,6-tetrahydropyridinyl.
8. The process according to claim 1 wherein the compound of formula (I) is (5S)-5-allyl-
10 2,2,4-trimethyl-2,5-dihydro-1H-chromeno[3,4-f]quinolin-10-yl trifluoromethanesulfonate.
9. The process according to claim 1 wherein in step (a) the hydroxy protecting group is selected from the group consisting of acetyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, methyldiphenylsilyl,
15 tert-butyldiphenylsilyl, tribenzylsilyl and triphenylsilyl.
10. The process according to claim 1 wherein in step (a) the hydroxy protecting group is tert-butyldimethylsilyl.
- 20 11. The process according to claim 1 wherein in step (a) the base is selected from the group consisting of sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide, sodium hydride, potassium hydride, lithium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide and sodium bis(trimethylsilyl)amide.
25
12. The process according to claim 1 wherein in step (a) the base is potassium tert-butoxide.
13. The process according to claim 1 wherein in step (b) the electrophile is selected from
30 the group consisting of acetyl chloride, propionyl chloride, trimethylacetyl chloride, dimethylcarbamyl chloride, allyl bromide, methyltriflate, methyltosylate, dimethylsulfate,

iodomethane, iodoethane, trifluoromethyl iodide, perfluoroethyl iodide, benzyl bromide, benzyl chloride, propargyl bromide, acetic anhydride, trifluoromethyl anhydride, di-tert-butyl dicarbonate, benzyl chloroformate, ethyl chloroformate, isopropyl chloroformate, methanesulfonyl chloride, para-toluenesulfonyl chloride, phenylsulfonyl chloride, trifluoro-
5 N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide and trifluoromethanesulfonic anhydride.

14. The process according to claim 1 wherein in step (b) the electrophile is selected from the group consisting of iodomethane and trifluoro-N-phenyl-N-
10 [(trifluoromethyl)sulfonyl]methanesulfonamide.

15. The process according to claim 1 wherein in step (c) the hydroxy deprotecting reagent is selected from the group consisting of tetrabutylammonium fluoride, potassium fluoride, hydrogen fluoride, hydrochloric acid, hydrobromic acid, acetic acid, trifluoroacetic acid, aqueous potassium hydroxide, aqueous sodium hydroxide, aqueous potassium carbonate and
15 aqueous sodium bicarbonate.

16. The process according to claim 1 wherein in step (c) the hydroxy deprotecting reagent is tetrabutylammonium fluoride.
20

17. The process according to claim 1 wherein in step (d) the azo reagent is selected from the group consisting of diethyl azodicarboxylate, di-tert-butyl azodicarboxylate, diisopropyl azodicarboxylate, dimethyl azodicarboxylate and dicyclohexyl azodicarboxylate; and the phosphine reagent is selected from the group consisting of tributylphosphine, tri-tert-butylphosphine, triisobutylphosphine, triisopropylphosphine, tripropylphosphine, triethylphosphine, trimethylphosphine, tris(4-methylphenyl)phosphine, tris(4-methoxyphenyl)phosphine, tris(4-chlorophenyl)phosphine, tris(4-bromophenyl)phosphine and triphenylphosphine.
25

18. The process according to claim 1 wherein in step (d) the azo reagent is diisopropyl azodicarboxylate; and the phosphine reagent is triphenylphosphine.
30

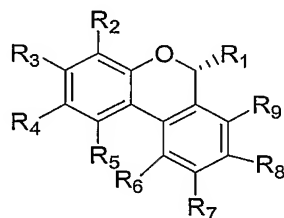
19. The process according to claim 1 wherein
in step (a) the compound of formula (Ia) is (1R)-1-[6-(2,6-bis{[tert-butyl(dimethyl)silyl]oxy}phenyl)-2,2,4-trimethyl-1,2-dihydroquinolin-5-yl]but-3-en-1-ol; the
5 base is potassium tert-butoxide; and the first solvent is tetrahydrofuran;
in step (b) the electrophile is iodomethane;
in step (c) the hydroxy deprotecting reagent is tetrabutylammonium fluoride; and the
second solvent is tetrahydrofuran; and
in step (d) the azo reagent is diisopropyl azodicarboxylate; the phosphine reagent is
10 triphenylphosphine; and the third solvent is tetrahydrofuran.
20. The process according to claim 19 wherein
step (a) is conducted from about -5 °C to about 25 °C.
- 15 21. The process of claim 20 further comprising isolating the product of step (b) by
pouring step (b) into saturated ammonium chloride solution; stirring the solution; separating
the aqueous phase from the organic phase; washing the organic phase with brine; drying the
organic phase over sodium sulfate; concentrating the organic phase to provide an oil;
dissolving the oil in heptane; extracting the heptane with acetonitrile; treating the heptane
20 with charcoal; and concentrating the heptane.
22. The process according to claim 21 wherein step (c) is conducted between 18 °C and
about 25 °C for about 12 to 36 hours.
- 25 23. The process according to claim 22 further comprising isolating the product of step (c)
by pouring step (c) into a saturated solution of ammonium chloride; stirring the solution;
adding tert-butyl methyl ether to the solution; stirring the solution for about 5 to 20 minutes;
separating the aqueous phase from the organic phase; washing the organic phase with brine;
drying the organic phase over sodium sulfate; concentrating the organic phase to provide a
30 solid; suspending the solid in isopropanol:heptane 1:12.5 for 1 to 3 hours; cooling the

isopropanol:heptane 1:12.5 to -5 °C to about 5 °C; and filtering the isopropanol:heptane 1:12.5.

24. The process according to claim 23 wherein in step (d) the product of step (c) and the triphenylphosphine are dissolved in the tetrahydrofuran at a temperature between about 18 °C and about 25 °C; the tetrahydrofuran is cooled to about -5 °C to about 15 °C; and the diisobutyl azodicarboxylate is added to the tetrahydrofuran over about 0.25 to 3 hours while maintaining the temperature of the tetrahydrofuran from about -5 °C to about 25 °C.

25. The process according to claim 24 further comprising isolating the product from step(d) by concentrating the tetrahydrofuran to about 1/4 to 1/3 of original volume; adding heptane to the tetrahydrofuran; cooling the tetrahydrofuran/heptane mixture to about -5 °C to about 5 °C; allowing the tetrahydrofuran/heptane mixture to stand for 12 to 24 hours; filtering the tetrahydrofuran/heptane mixture; repeating concentration, cooling and filtering until small amount of solid precipitates out of the tetrahydrofuran/heptane mixture; concentrating the tetrahydrofuran/heptane mixture to provide crude product of step (d); purifying the crude product of step (d) by flash chromatography to provide the product of step (d); and recrystallizing the product of step (d) from isopropanol.

26. A process for the preparation of a compound having formula (II)



(II),

wherein

R₁ is selected from the group consisting of alkenyl, alkyl, alkynyl and aryl;

R₂, R₃ and R₄ are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl and halogen; or

R_2 and R_3 or R_3 and R_4 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

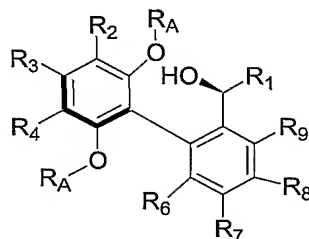
R_5 is selected from the group consisting of hydrogen, alkenyl, alkenyloxy, alkoxy, alkoxy-carbonyloxy, alkoxy-sulfonyloxy, alkyl, alkyl-carbonyloxy, alkyl-sulfonyloxy, alkynyl, alkynyloxy, aryl, arylalkoxy, arylalkoxy-carbonyloxy, arylsulfonyloxy, haloalkoxy, haloalkyl-carbonyloxy, haloalkyl-sulfonyloxy, halogen, heterocycle and $(NR_C R_D)$ -carbonyloxy; and

R_6 , R_7 , R_8 and R_9 are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl and halogen; or

R_6 and R_7 or R_7 and R_8 or R_8 and R_9 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

wherein said process comprises the steps of:

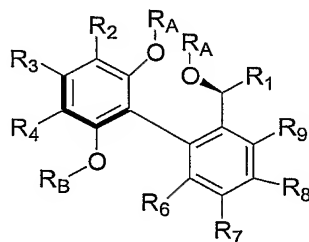
(a) treating a compound of formula (IIa) with a base in a first solvent



(IIa),

wherein R_A is a hydroxy protecting group and R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above;

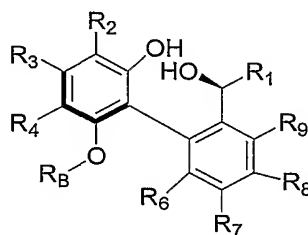
(b) treating the product of step (a) with an electrophile to provide a compound of formula (IIb)



(IIb),

wherein R_B is selected from the group consisting of alkoxy carbonyl, alkoxy sulfonyl, alkenyl, alkyl, alkyl carbonyl, alkyl sulfonyl, alkynyl, aryl alkoxy carbonyl, aryl alkyl, aryl sulfonyl, haloalkyl, haloalkyl carbonyl, haloalkyl sulfonyl and $(NR_C R_D)$ carbonyl wherein R_C and R_D are selected from the group consisting of hydrogen and alkyl; and R_A , R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above;

(c) treating the compound of formula (IIb) with a hydroxy deprotecting reagent in a second solvent to provide a compound of formula (IIc)

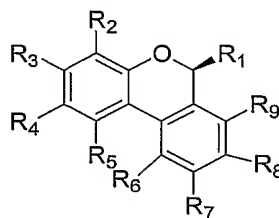


(IIc)

wherein R_B , R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 and R_9 are as defined above; and

(d) treating the compound of formula (IIc) with an azo reagent and a phosphine reagent in a third solvent.

27. A process for the preparation of a compound having formula (I)



(I),

wherein

R_1 is selected from the group consisting of alkenyl, alkyl, alkynyl and aryl;

R_2 , R_3 and R_4 are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

R_2 and R_3 or R_3 and R_4 together with the carbon atoms to which they are attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

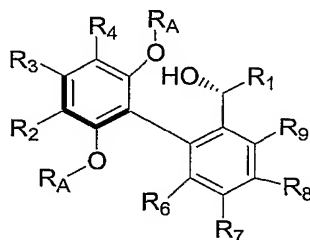
R₅ is selected from the group consisting of hydrogen, alkenyl, alkenyloxy, alkoxy, alkoxy-carbonyloxy, alkoxy-sulfonyloxy, alkyl, alkyl-carbonyloxy, alkyl-sulfonyloxy, alkynyl, alkynyloxy, aryl, arylalkoxy, arylalkoxy-carbonyloxy, aryloxy, arylsulfonyloxy, haloalkoxy, haloalkyl-carbonyloxy, haloalkyl-sulfonyloxy, halogen, heterocycle and (NR_CR_D)carbonyloxy
 5 wherein R_C and R_D are each independently selected from the group consisting of hydrogen and alkyl; and

R₆, R₇, R₈ and R₉ are each independently selected from the group consisting of hydrogen, alkoxy, alkenyl, alkyl, alkynyl, aryl and halogen; or

R₆ and R₇ or R₇ and R₈ or R₈ and R₉ together with the carbon atoms to which they are
 10 attached, together form a ring wherein the ring is selected from the group consisting of aryl, cycloalkyl and heterocycle;

wherein said process comprises the steps of:

(a) treating a compound of formula (Ia) with at least two molar equivalents of a hydroxy deprotecting reagent in a first solvent to provide a compound of formula (Ia)



(Ia),

wherein R_A is a hydroxy protecting group and R₁, R₂, R₃, R₄, R₆, R₇, R₈ and R₉ are as defined above, to provide a compound of formula (Ia) wherein R_A is hydrogen;

(b) treating the product of step (a) with an azo reagent and a phosphine reagent in a
 20 second solvent to provide the compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/19115

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D311/80 C07D491/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 41256 A (ABBOTT LAB ;LIGAND PHARM INC (US)) 19 August 1999 (1999-08-19) Scheme 1	1-27
A	WO 96 19458 A (LIGAND PHARM INC) 27 June 1996 (1996-06-27) Scheme XXV	1-27
A	WO 98 38193 A (MEDICHEM RESEARCH INC) 3 September 1998 (1998-09-03) Scheme IV	1-27



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

20 September 2002

Date of mailing of the international search report

27/09/2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 02/19115

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9941256	A	19-08-1999	AU 2677399 A	30-08-1999
			BG 104719 A	31-05-2001
			BR 9907788 A	30-10-2001
			CA 2320943 A1	19-09-1999
			CN 1296486 T	23-05-2001
			EP 1053239 A1	22-11-2000
			HU 0100460 A2	28-09-2001
			JP 2002503665 T	05-02-2002
			NO 20004053 A	11-09-2000
			PL 343018 A1	30-07-2001
			SK 11972000 A3	06-08-2001
			TR 200003094 T2	22-01-2001
			WO 9941256 A1	19-08-1999
			ZA 9901156 A	12-08-1999
WO 9619458	A	27-06-1996	US 5688810 A	18-11-1997
			US 5688808 A	18-11-1997
			US 5693647 A	02-12-1997
			US 5696127 A	09-12-1997
			US 5693646 A	02-12-1997
			US 5696130 A	09-12-1997
			US 5696133 A	09-12-1997
			AU 717251 B2	23-03-2000
			AU 4597796 A	10-07-1996
			BR 9510486 A	02-06-1998
			CA 2208347 A1	27-06-1996
			CN 1175247 A	04-03-1998
			CZ 9701761 A3	16-09-1998
			EP 1043325 A1	11-10-2000
			EP 1043326 A1	11-10-2000
			EP 1041071 A1	04-10-2000
			EP 1041066 A1	04-10-2000
			EP 1043315 A1	11-10-2000
			EP 0800519 A1	15-10-1997
			HU 78117 A2	29-11-1999
			JP 10510840 T	20-10-1998
			NO 972591 A	14-08-1997
			NO 20003534 A	14-08-1997
			NO 20003550 A	14-08-1997
			NO 20003551 A	14-08-1997
			NO 20003552 A	14-08-1997
			NZ 300739 A	26-05-2000
			WO 9619458 A2	27-06-1996
			US 6093821 A	25-07-2000
			US 5994544 A	30-11-1999
			US 6121450 A	19-09-2000
			US 6448405 B1	10-09-2002
WO 9838193	A	03-09-1998	US 6043271 A	28-03-2000
			WO 9838193 A1	03-09-1998
			US 5977385 A	02-11-1999
			US 6277879 B1	21-08-2001
			US 5892060 A	06-04-1999
			US 2002013478 A1	31-01-2002
			US 5872264 A	16-02-1999
			US 5981770 A	09-11-1999
			US 5847164 A	08-12-1998
			US 5874591 A	23-02-1999

INTERNATIONAL SEARCH REPORT

information on patent family members

In Additional Application No

PCT/US 02/19115

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9838193	A	US 5840921 A	24-11-1998
		US 5859050 A	12-01-1999
		US 5869324 A	09-02-1999
<hr/>			